

## NOVEL DELIVERY TECHNOLOGIES OF HRT

### Review of the Advantages and Disadvantages

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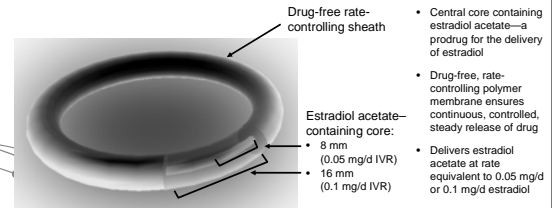
## Why are we looking at new delivery systems?

- More constant serum levels (less fluctuations)
- Equal effectiveness
- Fewer adverse events
- Improved compliance and patient acceptance
- Improved safety profile
- Lowest effective dose
- Target local uterine effect with local progestogen

## Novel Hormone Delivery systems

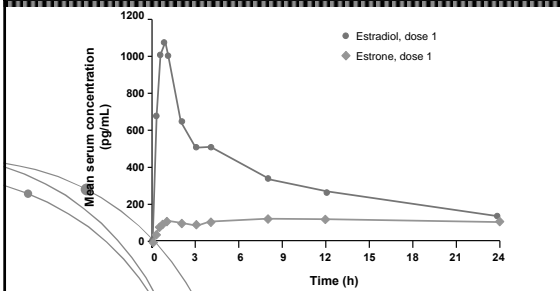
Estradiol acetate ring	Estrogen-progestin ring
Nasal estradiol	Sublingual estradiol
Estradiol gel	Estradiol pellets
Ultralow-dose estradiol	0.25 (oral), 0.014 (patch)
Progestogen IUDs	Progesterone vaginal gel
Transdermal Testosterone	

## Estradiol acetate ring delivery system



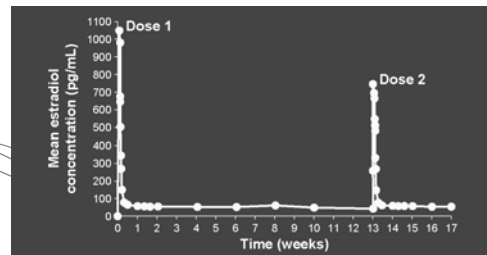
Al-Azzawi F, et al. Poster presented at British Menopause Society Congress, June 2001. Data on file, Warner Chilcott, Inc.

## Mean serum estradiol and estrone profiles: Estradiol acetate ring 0.05 mg/d

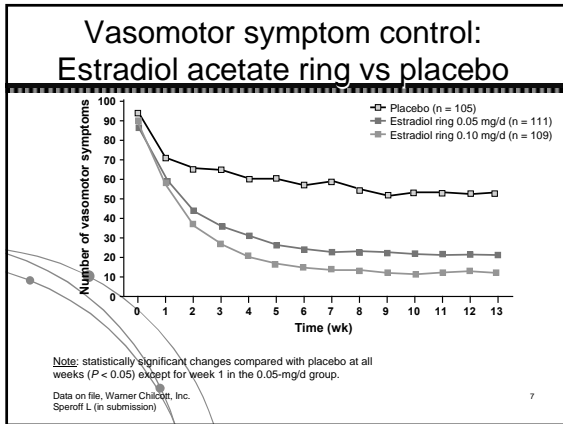


McNamee, de Vries. Poster presented at North American Menopause Society, October 2001.

## Mean serum estradiol profile: Estradiol ring 0.05 mg/d



Passmore et al. Poster presented at British Menopause Society Congress, June 2001.



### Estrogen ring: Patient complaints\*

Expulsion	7
Ring slippage	5
Discomfort and pressure	5
Discharge	22
Itch	11
Odor	7
Infection (vaginosis, yeast)	5
Tenderness / pain during intercourse	2

\*N = 70, 6-month trial.  
Nash et al. Am J Obstet Gynecol 1999;181:1400-1406.

### Sexual Activity\*

	Subjects (n)	%
Told partner of ring	1180	71.1
Partner felt ring	473	28.5
Partner had negative feelings	134	8.1
Ring interfered with sex	119	7.2
Patient had pain due to ring during sex	113	6.8
Partner had pain due to ring	30	1.8

\*Applies only to subjects who had sex while wearing the ring (n=1660).  
Data on file, Warner Chilcott, Inc.

- ### Estradiol acetate ring: Advantages
- FDA approved for vasomotor, vulvar, and vaginal symptoms
  - Effective for 3 months
  - Available in two strengths (0.05 and 0.1 mg/d)
  - Easily inserted/removed
  - High level of acceptability
  - Low level of expulsion

- ### Estrogen ring disadvantages
- Not indicated for osteoporosis
  - Vaginal irritation
  - Discomfort
  - Need for progestin
  - Expulsion

- ### Nasal Estradiol
- Aqueous nasal formulation of estradiol
    - 300 mg/day (150 mg per nostril/day)
  - Mucociliary absorption
  - Pharmacokinetics
    - Rapid absorption- high brief plasma estradiol peak
    - Rapid fall to 10% within 2 hours
    - Untreated level by 12 hours
  - Brief stimulation of estradiol receptors
    - leads to gene activation
- Gompel et al. Maturitas 2000;38:209-215; Mattsson et al. Am J Obstet Gynecol 2000;182:545-552; Devissaguet et al. Euro J Drug Metab Pharmacokin 1989;24:265-271; Ozsoy et al. J Gynecol Obstet 2002;79:143-146; Mattsson. Climacteric 2002;2(Suppl 5):40-45; Paleolos. Climacteric 2002;2(Suppl 5):32-39.

## Nasal estradiol: Advantages

- **Rapidly absorbed**
  - Avoids first-pass metabolism
- **Well tolerated**
  - 15% discontinuation at 1 year
- **Prevents bone loss**
  - equivalent to 2 mg oral or .50ug patch
- **Lower rates of withdrawal bleeding and mastalgia compared with oral therapy**
  - 4.4% (n=134) withdrew AE: 2 mastalgia, 1 headache, 1 permanent runny nose, 1 allergy and 1 nasal prickling  
Pelissier et al. *Maturitas* 2001;37:181-189.
- **Lower rate of tumor induction (animal models)**

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## Nasal estradiol: Disadvantages

- **Effectiveness in patients unknown with**
  - nasal pathology
  - allergies
  - nasal and sinus infections
- **Concern about effects of high bursts**

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## Sublingual micronized 17 beta-estradiol

- **Pharmacokinetics**
  - rapid, burst-like absorption
  - initial high estradiol levels fall rapidly during first 6 hours
- **Results in significantly higher estradiol levels at 24 hrs**
  - compared with 1 mg or 0.5 mg oral agents
- **Favorable decreases in urine markers of bone metabolism**
- **Slight increases in spine and hip BMD at 1 year**
- **Cardiovascular benefits in ischemia and LV function**

Price et al. *Gabest Gynecol* 1997;88:340-345.  
Miller et al. *Menopause* 2000;7:318-326.

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## Transdermal Overview Patches, gels, creams and rings

- **Consistent delivery**
- **Lower doses lead to therapeutic hormone levels**
- **Avoids first-pass metabolism**
- **Absorption varies according to carrier vehicle, application location**
- **Rapid onset and rapid termination of action**
- **Continuation and compliance may be improved**
- **Dosages can be self-controlled (for some gels)<sup>1</sup>**
- **Stable HDL and triglyceride levels**

1. Vihtamaki et al. *Eur J Endocrinol* 2002;146:333-338.

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## Medical indications for transdermal estradiol

- **Smokers**
- **Alcoholics**
- **Liver disease, gallbladder disease**
- **Hyperinsulinemia**
- **Elevated triglyceride levels**
- **Poor control of symptoms**
- **Lactose intolerance**

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## 17 B Estradiol gel

- **Estradiol is suspended in a hydro-alcoholic gel**
- **Available in France for 20 years and Canada for 4**
- **In the US, will be available as pump-metered dose**
  - 1.5 mg (equiv. of 0.5 mg oral estradiol)
  - 2.5 mg (equiv of 1.0 mg)
- **Physiologic plasma concentrations of estradiol**
- **Steady state bioavailability is 82% compared with equivalent oral dose**

www.healthanswers.com.au/drugdata  
Moogani S et al. *J Clin Endo Metab*  
1991;73:373-379

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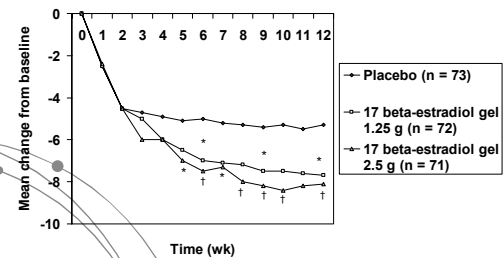
## 17 B Estradiol gel

- Skin acts as an intradermal reservoir and rate-controlling membrane
  - apply to a large surface area (wrist to shoulder) for maximal absorption
  - apply day 1-21/28-day cycle on both arms, abdomen, or inner thighs (similar rates of absorption)
  - Vehicle evaporates in 2 to 4 minutes leaving no residue (nonsticky, no odor)

www.xcanadapharmacy.com  
www.healthanswers.com.au/drugdata

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## Reduction of vasomotor symptoms with 17 beta-estradiol gel



\*P < 0.05 vs placebo; †P < 0.001 vs placebo.  
Adapted from data on file (Solvay).

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## 17 B Estradiol gel: Advantages

- Equivalent to oral and transdermal (patch) therapies in vasomotor relief
- Avoids first-pass hepatic metabolism
  - 1% increase triglycerides vs 34% with CEE
  - No increase in renin substrate or SHBG
- Increased BMD similar to CEE in lumbar spine (+5.6% vs +4.1%)
- Skin irritation considerably lower (1.1%)
- 97% rate gel as acceptable or convenient

Hirvonen et al. *Climacteric* 2000;3:262-270.  
Nunez M. *Obstet Gynecol* 2000;95(suppl 1):S23 abstract  
Moorjani S, et al. *JCEM* 1991;73:373-379

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## Estradiol gels: Disadvantages

- Lacking long term safety data
- No fracture prevention data
- Need progestogen protection for uterus

Hirvonen et al. *Climacteric* 2000;3:262-270.  
www.healthanswers.com.au/drugdata

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## Declining dosages of estrogen

Genant 1982 Lindsay 1984	0.525 mg conjugated equine estrogen appears ineffective (younger oophorectomized women)
Ettinger 1992, Evans 1996, Genant 1997, Recker 1999, Delmas 2001, Lindsay 2002	0.3 mg conjugated estrogen or equivalent preserves bone
Prestwood 2009, 2003	0.25 µg micronized 17 β-estradiol has effects on bone similar to 1.0 mg/d with a lower side effect profile
Ettinger (in submission)	0.014 mg/d via transdermal patch benefits bone density in postmenopausal women

Genant et al. *Ann Intern Med* 1982;97:699-705.  
Lindsay et al. *Obstet Gynecol* 1984;63:759-763.  
Ettinger et al. *Am J Obstet Gynecol* 1992;166:479-488.  
Evans, Davie. *Clin Endocrinol* 1996;44:79-84.  
Genant et al. *Arch Intern Med* 1997;157:2609-2615.  
Recker et al. *Ann Intern Med* 1999;130:897-904.  
Delmas et al. *Am J Obstet Gynecol* 2001;184:32-40.  
Lindsay et al. *JAMA* 2002;287:2668-2676.  
Prestwood et al. *J Clin Endocrinol Metab* 2000;85:4462-4469.  
Ettinger (in submission).

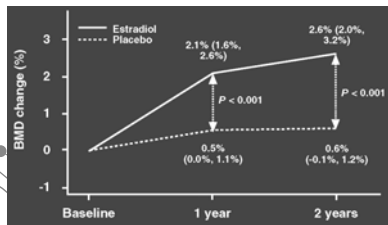
## Ultralow-dose estradiol: Transdermal 0.014 estradiol patch

- Design
  - 2-year, double-blind, placebo-controlled, multicenter trial
  - 417 postmenopausal women 60 to 80 (mean, 67±5)
- Intervention
  - Placebo (n = 209)
  - 0.014 mg/d estradiol patch (n = 208)
  - 800 mg/d calcium, 400 IU vitamin D
- End points
  - Hip and spine bone mineral density at 2 years
  - Endometrial evaluation

Ettinger (in submission).

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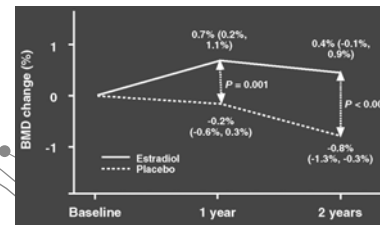
### Ultralow-dose estradiol patch: Effects on lumbar spine BMD



Ettinger (in submission)

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### Ultralow-dose estradiol patch: Effects on hip BMD



Ettinger (in submission)

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### Ultralow-dose estradiol patch: Advantages

- Improves bone density in older women
- Does not increase rates of endometrial hyperplasia at 2 years
- Need exists for a revised definition of estradiol sufficiency in older women

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### Ultralow dose therapies Disadvantages

- Not as effective in treating vasomotor symptoms or preventing bone loss
- Theoretically safer (no data)
- Lack of long term safety and efficacy
  - risk of breast cancer, endometrial cancer and fracture

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### Nonoral progestogen delivery

- Estrogen and progestogen patches and rings
- Levonorgestrel IUD 20 µg, 10 µg
- Vaginal progesterone gel : 4%, 8%

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### Levonorgestrel IUD compared with oral medroxyprogesterone acetate

	Levonorgestrel		
	10 µg IUD	20 µg IUD	Oral medroxyprogesterone acetate
Endometrial suppression after 12 mo	97.9%	100%	38.1%
Endometrial hyperplasia after 12 mo	0%	0%	0%
Bleeding after 6 mo	95.6%	98.2%	Typical cyclic withdrawal bleeding

Raudaskoski et al. Br J Obstet Gynaecol 2002;109:136-144.

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### 10 µg vs 20 µg levonorgestrel IUD: Ease of insertion

- **10 µg**
  - Easy in 70%
  - Difficult in 4%
- **20 µg**
  - Easy in 46%
  - Difficult in 21%

Raudaskoski et al. Br J Obstet Gynaecol 2002;109:136-144.

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### Progesterone IUD: Side effects

- **Rare**
  - Cervical perforation or laceration
  - Embedment of IUD
  - Device fragmentation
  - Neurovascular episodes (at time of insertion)
  - Pelvic inflammatory disease
- **Less rare**
  - Abdominal pain or cramping upon insertion
  - Continuing uterine bleeding on insertion
- **Postmenopausal women-** difficulty with insertion

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### Intrauterine devices: Advantages

- **Cost-effective**
- **Assured compliance**
- **Local effects instead of systemic reversible effects**
- **Long-term single-dose therapy (1 to ≥5 years)**

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### Vaginal progesterone gel

- **Progesterone is absorbed orally**
  - >90% metabolized during first-pass effect
  - high levels of progesterone metabolites lead to increased drowsiness and dizziness
- **Not well absorbed through skin**
- **Progesterone vaginal (polycarophil) gel**
  - controlled and sustained release properties
  - local direct vaginal uptake
    - Results in preferential uterine uptake
  - plasma levels remain physiologic
  - endometrial changes produced

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### Progesterone vaginal gel—4%, 8%

- **Multicenter, randomized, parallel, open-label 3-month trial**
  - 127 women with secondary amenorrhea; qod x 6 doses
- **Progestational changes on endometrial biopsy**
  - 4% gel: 92%
  - 8% gel: 100%
- **Compliance >98%**
- **Most side effects decreased**

Warren et al. Am J Obstet Gynaecol 1999;180:42-48.

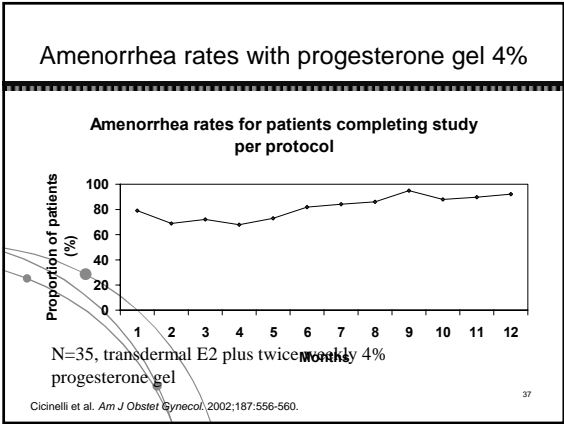
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### Transdermal estradiol and vaginal progesterone gel: 1-year trial

- **Prospective observational trial**
  - 26/ 35 (74.3%) women completed
- **Blood pressure and weight dropped significantly at month 3 and remained lower**
- **100% amenorrheic at 1 year**
- **Endometrial thickness significantly greater than baseline at 1 year**
  - Baseline 3.6 mm (+/-0.9), endometrial atrophy in all
  - 12 months, 4.6 mm (+/- 0.9mm),
  - endometrial atrophy 92.3%

Cicinelli et al. Am J Obstet Gynaecol 2002;187:556-560.

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- ### Estrogen plus vaginal progesterone gel: cyclic vs continuous
- **Continuous estrogen**
    - + cyclic progesterone vaginal gel 4% days 1-10 (69 women)
    - + continuous progesterone vaginal gel 4% twice weekly (67 women)
  - **At 6 months**
    - **Cyclic therapy**
      - 63 (91.9%) predictable withdrawal bleeding
    - **Continuous therapy**
      - 54 (80.6%) amenorrheic
- de Ziegler et al. *Hum Reprod* 2000;15:149-158.

- ### Progesterone gel Advantages and Disadvantages
- **Advantages**
    - plasma levels remain physiologic
    - local direct vaginal uptake
      - results in preferential uterine uptake
    - Fewer side effects
    - Theoretically less systemic effects
  - **Disadvantages**
    - Lack of long term efficacy and safety data with regards to protection against endometrial cancer

### Transdermal Testosterone Treatment in Women with Impaired Sexual Function After Oophorectomy

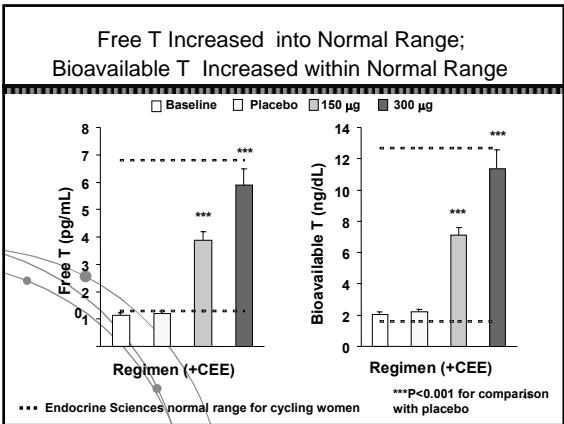
- **Design**
  - Multi-center, double-blind, randomized, placebo-controlled, crossover study
  - Three treatment periods

Screen/Baseline	Period I	Period II	Period III
4wk	12 wk	12 wk	12 wk

• **Treatment Regimens**

- All patients maintained on oral CEE (≥ 0.625 mg) during study, with twice weekly application of placebo or testosterone patches
- CEE + 0 µg/day testosterone (2 placebo patches)
- CEE + 150 µg/day testosterone (1 testosterone/1 placebo patch)
- CEE + 300 µg/day testosterone (2 testosterone patches)

Shiffren J. *NEJM* 2000; 343, p.682-688.



- ### Treatment of surgically menopausal women with transdermal testosterone:
- Significantly increased frequency of sexual activity, pleasure/orgasm (BISF-W), and psychological well-being (PGWB) at higher testosterone dose
  - Well tolerated locally and systemically
    - no clinically significant effects on hirsutism, acne, cholesterol, glucose or insulin levels
  - Increased free and bioavailable testosterone in dose-dependent manner within physiologic range
  - Did not alter estrogen concentrations

### Bioidentical/compounded hormones

- **Advantages**
  - 'natural'
  - 'milder'
  - 'safer'
- **Disadvantages**
  - Lack safety/efficacy data
  - Lack long term data
  - Concern about batch to batch variability or contamination
  - Not FDA approved, not regulated

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### Novel delivery technologies of HRT

- **Estradiol vaginal ring**
  - - sustained levels for 3 months
- **Nasal/sublingual estradiol**
  - - high brief estradiol peak
- **17 B estradiol gel-**
  - Skin acts as intradermal reservoir + rate-controlling membrane
- **Ultra low estradiol- patch (0.014)-**
  - maintain BMD without uterine stimulation at 2 years
- **Progestogen IUDs**
  - - sustained local uterine effect
- **Progesterone vaginal gel**
  - More local effect, fewer side effects

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### Novel Technologies of HRT

- **Effective at reducing vasomotor symptoms**
- **Maintain BMD**
- **Potential for fewer side effects**
  - -less fluctuations in levels
- **Increased compliance and patient acceptance**
- **Avoid first-pass hepatic effects**

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### Conclusion: novel technologies

- **How important is the route of administration?**
  - Do they meet the goal of sustained levels with little fluctuation?
  - Advantage to bypassing first-pass hepatic effect?
- **What is the lowest effective dose of estrogen?**
- **Is the lowest dose dependent on**
  - delivery system?
  - women's age?
  - her baseline estradiol?
- **Is different safer or better?**

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Dr. JoAnn Pinkerton – Questions & Answers

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